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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HUTSON, RICHARD G	

ART UNIT	PAPER NUMBER
1652	16

DATE MAILED: 11/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	10/018,113	KELLER ET AL.	
	Examiner	Art Unit	
	Richard G Hutson	1652	

-- The MAILING DATE of this communication appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants amendment canceling claims 11-15, Paper No. 10, 2/27/2003, is acknowledged. Claims 1-101 are still at issue and are present for examination.

Election/Restrictions

Applicant's election without traverse of Group I, Claims 1-10 in Paper No. 10 is acknowledged.

Priority

Applicants This application is recognized as a national stage application of International Application PCT/DE00/01950 filed June 15, 2000, which claims priority to German Application 199 28 313.3, filed June 16, 1999.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper."

Applicants filing of information disclosures, Paper No. 4, filed 3/5/2002, is acknowledged. Those references considered have been initialed.

Specification

The disclosure is objected to because of the following informalities:

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth: The following portions of the specification list sequences which appear to meet the definition for a amino acid sequence, but do not have an associated SEQ ID No: page 4, line 32, page 5, line 2, page 8, lines 4-10, page 10, 1-16, page 12, lines 1-21, page 19, Table 2, page 20-21 and Figure 3.

Additionally, applicants attention is drawn to the M.P.E.P. Section, **2422.02** The Requirement for Exclusive Conformance; Sequences Presented in Drawing Figures 37 CFR 1.821(b) which states:

> ...It should be noted, though, that when a sequence is presented in a drawing, regardless of the format or the manner of presentation of that sequence in the drawing, the sequence must still be included in the Sequence Listing and the **sequence identifier ("SEQ ID NO:X") must be used, either in the drawing or in the Brief Description of the Drawings**.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-3 (claims 4-10 dependent on) are indefinite in that they are each worded in such a way that the claims are difficult to read and thus vague and confusing. As an example claim 1 recites :

1. Method for the manufacture of a recombinant DNA encoding for a polypeptide synthetase (PPS) activation domain with N-methyltransferase activity, wherein a first DNA fragment encoding for a domain with N-methyltransferase activity is cloned into a second DNA fragment encoding for a PPS activation domain without N-methyltransferase activity, and wherein the first and the second DNA fragment form a continuous reading frame.

Claim 1 is interpreted as and it is suggested that the claim be amended such as:

1. **A** method for the manufacture of a recombinant DNA **which** encod[ing]**es** [for] a polypeptide synthetase (PPS) activation domain with N-methyltransferase activity, wherein a first DNA fragment **which** encod[ing]**es** [for] a **PPS activation** domain with N-methyltransferase activity is cloned into a second DNA fragment **which** encod[ing]**es** [for] a PPS activation domain without N-methyltransferase activity, and wherein the first and the second DNA fragment form a continuous reading frame.

It is also suggested that the method claims 2-6, 9 and 10 and the DNA and cell claims, 7 and 8 respectively, be amended such as is suggested for claim 1 above, such

that the claims are clearer with respect to the claimed invention. Applicants attention is further directed to the proper use of "encodes" versus "encoding".

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-10 are directed to all possible methods for the manufacture of recombinant DNAs which encode a polypeptide synthetase (PPS) activation domain with N-methyltransferase activity, wherein a first DNA fragment which encodes any domain with N-methyltransferase activity is cloned into a second DNA fragment which encodes a PPS activation domain without N-methyltransferase activity, and wherein the first and the second DNA fragment form a continuous reading frame and all possible DNAs and cells containing said DNAs, wherein said DNA is obtainable by said methods. The specification, however, only provides the representative methods comprising the manufacture of a recombinant DNA which encodes a polypeptide synthetase (PPS) activation domain with N-methyltransferase activity, wherein a DNA fragment which encodes the activation domain with N-methyltransferase activity from actinomycin synthetase III (ACMS III) is cloned into a second DNA fragment which encodes a PPS

activation domain without N-methyltransferase activity. There is no disclosure of any particular structure to function/activity relationship in the single disclosed species. The specification also fails to describe additional representative species of these domains with N-methyltransferase activity by any identifying structural characteristics or properties other than N-methyltransferase activity, for which no predictability of structure is apparent. Given this lack of additional representative species as encompassed by the claims, applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 1-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for the manufacture of a recombinant DNA which encodes a polypeptide synthetase (PPS) activation domain with N-methyltransferase activity, wherein a first DNA fragment which encodes the activation domain with N-methyltransferase activity from actinomycin synthetase III (ACMS III) is cloned into a second DNA fragment which encodes a PPS activation domain of actinomycin synthetase II (ACMS II) and wherein the first and the second DNA fragment form a continuous reading frame, does not reasonably provide enablement for any method for the manufacture of recombinant DNA which encodes a polypeptide

synthetase (PPS) activation domain with N-methyltransferase activity, wherein a first DNA fragment which encodes any domain with N-methyltransferase activity is cloned into a second DNA fragment which encodes a PPS activation domain without N-methyltransferase activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 1-10 are so broad as to encompass any method for the manufacture of a recombinant DNA which encodes a polypeptide synthetase (PPS) activation domain with N-methyltransferase activity, wherein a first DNA fragment which encodes any domain with N-methyltransferase activity is cloned into a second DNA fragment which encodes a PPS activation domain without N-methyltransferase activity. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of domains with N-methyltransferase activity broadly encompassed by the claims. The claims rejected under this section of U.S.C. 112, first paragraph, do not place any structural limits on the claimed domains and their

encoding DNAs. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the method for the manufacture of a recombinant DNA which encodes a polypeptide synthetase (PPS) activation domain with N-methyltransferase activity, wherein a first DNA fragment which encodes the activation domain with N-methyltransferase activity from actinomycin synthetase III (ACMS III) is cloned into a second DNA fragment which encodes a PPS activation domain of actinomycin synthetase II (ACMS II) and wherein the first and the second DNA fragment form a continuous reading frame.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any domain with N-methyltransferase activity, because the specification does not establish: (A) regions of the domain structure which may be modified without effecting N-methyltransferase activity; (B) the general tolerance of N-methyltransferase domains to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue of a N-methyltransferase domain with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Because of this lack of guidance, the extended experimentation that would be required to determine which substitutions would be acceptable to retain the N-methyltransferase activity and the fact that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), it would require undue experimentation for one skilled in the art to arrive at the majority of those methods, DNAs and cells of the claimed genus maintaining, encoding or comprising the claimed N-methyltransferase activity.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including the modification of any N-methyltransferase domain. The scope of the claims must bear a reasonable correlation

with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-10 are rejected under 35 U.S.C. 102(a) as being anticipated by Schauwecker et al. (Chemistry and Biology, Vol 7, No 4, pp 287-297, 3/2000).

Schauwecker et al. a method for the manufacture of a recombinant DNA which encodes a polypeptide synthetase (PPS) activation domain with N-methyltransferase activity, wherein a first DNA fragment which encodes the PPS activation domain with N-methyltransferase activity of actinomycin III (ACMS III) is cloned into a second DNA fragment which encodes the PPS activation domain without N-methyltransferase activity of actinomycin II (ACMS II), and wherein DNAs form a continuous reading frame and the resulting DNA and host cells containing said DNAs.

Remarks

No claim is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G Hutson whose telephone number is (703) 308-0066. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (703) 308-3804. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Richard G Hutson, Ph.D.
Primary Examiner
Art Unit 1652

rgh
10/31/2003